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Glucose-6-phosphate dehydrogenase deficiency

Synonyms: G6PD/G-6-PD deficiency, non-spherocytic haemolytic anaemia

The enzyme glucose-6-phosphate dehydrogenase (G6PD) is one of the enzymes of the pentose phosphate pathway. This pathway is involved in keeping an adequate amount of the coenzyme nicotinamide adenine dinucleotide phosphate (NADPH) in cells. NADPH in turn maintains the levels of glutathione which protects the red cell from oxidative damage. G6PD is the rate-limiting enzyme in the pentose phosphate pathway. Thus, deficiency of the G6PD enzyme results in reduced glutathione making the red cells vulnerable to oxidative damage and thus liable to haemolysis.

Pathophysiology

The disease is X-linked with about 300 variants reported. Most of the variants occur sporadically and are single amino acid defects in a protein of 515 amino acids.

Classes of G6PD deficiency enzyme variants [1]

- Severe (I) - chronic non-spherocytic haemolytic anaemia.
- Severe (II) - less than 10% of normal enzyme activity.
- Moderate (III) - 10-60% of normal enzyme activity.
- Mild to none (IV) - 60-150% of normal enzyme activity.
- None (V) - greater than 150% of normal enzyme activity.

More detailed information about variants is available under the Online Mendelian Inheritance in Man (OMIM) listing [2] .

Epidemiology

- Most individuals with the G6PD defect are asymptomatic and unaware of their status.
- About 400 million people are affected worldwide[3] . Gene frequency is between 5% and 25% in tropical Africa, the Middle East, tropical and subtropical Asia, some areas of the Mediterranean, and Papua New Guinea[1] . This makes it the most common disease-producing enzyme deficiency in the world.
- It affects all races but is most common in those of African, Asian or Mediterranean descent. It tends to be milder in those of African origin and more severe in the Mediterranean races.
- The epidemiology of G6PD deficiency has been noted to be remarkably similar to that of malaria, adding support to the 'malaria protection hypothesis'. Also, in vitro work has shown that malarial parasites grow slowest in G6PD-deficient cells[4] .
- Being X-linked, the disease affects mainly men but in areas of high frequency it is not uncommon to find homozygous women.

Factors that precipitate haemolytic crises

- Certain drugs (see below)

Drugs to watch out for in G6PD-deficient individuals	
Drugs with definite risks	**Drugs with possible risks**
Primaquine - although 30 mg weekly for eight weeks has been found to be without unduly harmful effects in African and Asian people Methylthioninium chloride (methylene blue) Nitrofurantoin and quinolones including ciprofloxacin, moxifloxacin, nalidixic acid, norfloxacin, and ofloxacin Sulfonamides including co-trimoxazole, although some sulfonamides like sulfadiazine have been tested and found not to be haemolytic in many with G6PD deficiency Dapsone EMLA® cream (prilocaine)	Aspirin - although a dose up to 1 g daily is usually harmless Chloroquine and quinine but they may be used in acute malaria Vitamin K analogues like menadione and water-soluble derivatives like menadiol sodium phosphate Sulfonylureas

- Certain foods (eg, eating broad beans) can lead to favism.
- Severe infection.
- Diabetic ketoacidosis.
- Acute kidney injury (can lead to a severe crisis).

The extent of haemolysis may vary across individuals, due to genetic heterogeneity. Despite this the extent of haemolysis is dose-dependent.

Presentation

History

- Depends upon the severity of the enzyme deficiency.
- Most are asymptomatic.

- May be a history of neonatal jaundice, severe enough to require exchange transfusion.
- History of drug-induced haemolysis.
- Gallstones are common.

Examination

- Most often, examination is unremarkable.
- Pallor of anaemia.
- During a crisis jaundice occurs.
- Back or abdominal pain (usually occurs when >50% haemolysis occurs).
- Splenomegaly may occur.

Investigations

- FBC - anaemia.
- Macrocytosis - due to reduced folic acid which is required for erythropoiesis.
- Reticulocyte count - raised; gives indication of the bone marrow activity (bone marrow sampling thus not needed).
- Blood film - acute haemolysis from G6PD deficiency can produce Heinz bodies, which are denatured haemoglobin and bite cells (cells with Heinz bodies that pass through the spleen have part of the membrane removed).
- Haemolysis - reduced levels of haptoglobin and elevated levels of bilirubin; haemoglobinuria.
- Direct antiglobulin test - to look for other causes of haemolysis; should be negative in G6PD deficiency.
- Renal function - to ensure no renal failure as a precipitant.
- LFTs - to exclude other causes of raised bilirubin.
- G6PD enzyme activity - is the definitive test (as opposed to the amount of G6PD protein).

- Performing assays for G6PD during haemolysis and reticulocytosis may affect levels and not reflect baseline values.
- Ultrasound examination of the abdomen may reveal splenomegaly and gallstones.

Management

Avoidance of substances that may precipitate haemolysis is essential. Usually no further management is required, although if haemolysis is marked there may be benefit from folate supplementation.

Management of acute haemolysis

- Seek specialised advice.
- Blood transfusions may be needed.
- Dialysis may be required in acute kidney injury.
- Infants - more susceptible to neonatal jaundice, especially if premature, and exchange transfusion may be required.

Management of chronic haemolysis or stable disease

- Splenectomy may help.
- Supplementation with folic acid.
- Avoidance of precipitating drugs, and broad beans (usually favism occurs in the Mediterranean variety of the disease).
- Avoid naphthalene - found in mothballs.

Complications and prognosis

Most people with G6PD deficiency have a normal life expectancy despite a predisposition to neonatal jaundice and sensitivity to certain drugs. If neonatal jaundice is not energetically treated, there may be a hidden risk for kernicterus [5] . However, G6PD activity is higher in premature infants born between 29 and 32 weeks of gestation than in term neonates [6] . Even if G6PD deficiency is anticipated, prophylactic oral phenobarbital given to the baby after delivery does not decrease the need for phototherapy or exchange transfusions in G6PD-deficient neonates [7] . Sn-mesoporphyrin (SnMP) is a potent inhibitor of bilirubin production that is effective in moderating neonatal hyperbilirubinaemia caused by ABO incompatibility, immaturity, and unspecified mechanisms, and may also help in G6PD deficiency. There is no definite association between G6PD deficiency and susceptibility to cataracts.

Although the disease is thought to be fairly benign, where enzyme levels are severely deficient there can be inadequate leukocyte function also. This results in chronic granulomatous disease [2] .

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